



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION

TECH CENTER 1600/2900

JAN 23 2002

RECEIVED

#14
JRP
2/1/02

In re application of

Masamichi OKADA, et al.

Appln. No.: 09/601,505

Group Art Unit: 1614

Confirmation No.: Unassigned

Examiner: FAY, Z

Filed: August 2, 2000

For: REMEDIES FOR CEREBRAL INFARCTION

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith is an executed Declaration Under 37 C.F.R. §1.132 signed by

Masamichi OKADA.

Respectfully submitted,

Drew Hissong
Registration No. 44,765

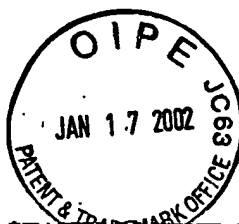
SUGHRUE MION, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

Date: January 17, 2002

2002年 1月17日 11時02分

山之内製薬株式会社

. 0448 P. 2/19



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED
JAN 23 2002
TECH CENTER 1600/2900

In re application of

Masamichi OKADA, et al

Appln. No.: 09/601,505

Confirmation No.: Unassigned

Group Art Unit: 1614

Filed: August 2, 2000

Examiner: FAY, Z

For: REMEDIES FOR CEREBRAL INFARCTION

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Masamichi OKADA, hereby declare and state:

THAT I am a citizen of Japan;

THAT I received a Bachelor's of Science in Chemistry from Tokyo Institute of Technology in March 1980, a Masters of Science in Neurochemistry from Tokyo Institute of Technology, in March 1982, and a Doctorate in Neurochemistry in 1985 from Tokyo Institute of Technology;

THAT I have been employed by Yamanouchi Pharmaceutical Co., Ltd., since 1985 where I hold a position as Research Scientist in the Neuroscience Research Laboratories, Institute for Drug Discovery Research, at Yamanouchi Pharmaceutical Co., Ltd.

I am familiar with claims 3-8 pending in the present application.

2002年 1月17日 11時02分

山之内製薬 波研センター

0448 P. 3/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appln. No. 09/601,505

Q60247

I am familiar with the knowledge of one skilled in the art of Molecular Biology and Neurochemistry, as of the March 3, 1998, filing date of the priority application JP 10-050241, which I understand corresponds to the pending application.

I have reviewed the Office Actions dated July 17, 2001, and January 29, 2001, in the above-identified application, and specifically the Examiner's rejection of claim 3 under 35 U.S.C. §102(b) as anticipated by Japanese Application No. 8-169884 ("JPA '884"), and claims 4-8 under 35 U.S.C. §103 as being obvious over JPA '884.

In order to demonstrate that the present invention is not anticipated by, or obvious over, the disclosure of JPA '884, I further declare and state the following.

I. Error in translation of U.S. national stage application

I first declare and state that an error was made in the translation of PCT application PCT/JP99/00995, prepared and filed in Japanese, into the English language and filed as the present application in the United States under 35 U.S.C. §371.

As found throughout the U.S. national stage application, the term "cerebral infarction" is used to refer to the condition for which the novel medicaments of the present invention are recited (see Disclosure of Invention, page 6, lines 5-6). The U.S. application also uses the term "cerebral infarction at the acute stage" (see page 6, lines 21-22). However, in the course of considering Examiner's rejections, I noticed that these English terms are not appropriate because these terms do not distinguish the two meanings involved in the corresponding Japanese word.

In general, the original Japanese term is used as the name of the disease, i.e., ischemic stroke. Ischemic stroke is a disease caused by an ischemic event which is a condition of oxygen

2002年 1月17日 11時02分

山之内薬 脳神経センター

0448 P. 4/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

deficiency in a part of the brain due to an interrupt of blood flow by thrombotic and/or embolic occlusion of cerebral artery and causes consequent neurological symptoms. If the occlusion is maintained to be enough to induce neuronal damage (longer than 1 h), an infarct (localized area of irreversible damage due to the occlusion of the artery supplying the area) may form.

Continued blood flow interruption can lead to the progression of the infarct to surrounding neuronal cells. Injury of the neuronal cells that control certain function causes the corresponding functional disorder as a sequela in the chronic stage of ischemic stroke.

The period of time shortly after the ischemic event induced by the occlusion of cerebral artery is term "acute stage ischemic stroke." If the interruption persists, neuronal tissue begins to be irreversibly damaged, i.e., a cerebral infarct forms. Regions of neuronal damage are referred to as "cerebral infarct" and the pathological condition which exists cerebral infarct is called "cerebral infarction". Thus, after the occlusion of cerebral artery, a subject is considered to have a disease ("ischemic stroke") that may, if not immediately corrected, lead to a pathological condition ("cerebral infarction").

The Japanese term used in the PCT application has both meanings of the disease ("ischemic stroke") and the pathological condition ("cerebral infarction"). However, as explained above, in the English language, two different terms are used. The literal translation of the Japanese term means "cerebral infarction at the acute stage." Because the terms is used for categorizing the disease based on the passage of time, it should have been translated into "acute (stage) ischemic stroke."

2002年 1月17日 11時03分

山之内製薬株式会社

0448 P. 5/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appln. No. 09/601,505

Q60247

The U.S. specification provides support for the use of the term "ischemic stroke" at page 6, line 2, where "human ischemic stroke" is disclosed.

Thus, where "acute stage cerebral infarction" is used in the specification and claims of the U.S. application, the term "acute stage ischemic stroke" should more accurately be used. The specification and claims are being amended accordingly.

II. Acute stage ischemic stroke and sequelae caused by cerebral infarction are two separate and different conditions

It had been recognized by persons skilled in the art that acute stage ischemic stroke and sequelae caused by cerebral infarction are two separate and different conditions, and that agents for treating acute stage ischemic stroke are different from those used to treat sequelae caused by cerebral infarction. Indeed, the skilled artisan would not reasonably expect that an agent for treating one condition could be used effectively in the treatment of the other condition.

The details of each condition, and the differences between them, are explained below.

A. Acute stage ischemic stroke

Acute stage ischemic stroke is understood by the skilled artisan to mean the period of time within 1 week after the onset of the ischemic stroke. *Neurology* 47:383-387 (1996). *

The treatment of acute stage ischemic stroke is undertaken to inhibit that expansion of neuronal cell death from the ischemic core region (i.e., the region which has the highest ischemic severity due to the dependence on the blood flow from the occluded artery and which is most liable to sustain damage resulting in the patient developing irreversible disorders) to the surrounding reversible region (penumbra). Thus, the primary object of any treatment during

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

acute stage ischemic stroke is the inhibition of the expansion of the infarct region, caused by acute neuronal cell death, that occurs within several hours after onset of ischemic stroke.

Therefore, it is quite important for the treatment agent of acute stage ischemic stroke to be administered as early as possible in order to inhibit the expansion of the infarct region. Administration of treatment agents within 48 hours at the latest, preferably within 6 hours, of the occurrence of the ischemic stroke is required. *Neurology* 47:383-387 (1996); *Lancet* 352 (suppl. III):10-14 (1998).

The clinical effects of the treatment on the inhibition of infarct region expansion is generally evaluated by diagnostic imaging utilizing CT and MRI. *Lancet* 352 (suppl. III):5-9 (1998). In addition, clinical symptoms that reflect the inhibition of infarct region expansion may be evaluated and include improvements in neurological symptoms, improvements in the disorders of daily life activities and improvements in motor paralysis.

For example, a Phase III double-blind study was carried out to evaluate the effects of tirilazad mesylate in the treatment of acute stage ischemic stroke. Therein, 191 patients with acute ischemic stroke (within 6 hours after the onset of ischemic stroke) were given tirilazad mesylate, intravenously administered for 3 days (6 mg/kg per day). Evaluation of the effects of the drug included CT findings at 6 to 11 days after the onset of ischemic stroke, as well as review of improvement in neurological symptoms, disorders in daily life activities and motor paralysis in each patient at 3 months after the stroke. *Stroke* 27:1453-1458 (1996).

Similar studies were conducted on the effects of giving Alteplase (t-PA), approved in the United States for treating acute ischemic stroke, to patients in a single intravenous administration

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

of 0.9 mg/kg within 3 hours after a stroke. The evaluated items included CT findings at 24 hours, 7 to 10 days, and 3 months after the stroke, as well as review of neurological symptoms at 3 months after the stroke, disorders in daily life activities and motor paralysis. *Stroke* 31:2912-2919 (2000); *New Eng. J. Med.* 333:1581-1587 (1995). /

B. Cerebral infarction sequelae

In contrast, sequelae caused by cerebral infarction is a group of neuropsychiatric and neuroethological disorders which are found in the chronic stage of ischemic stroke.

Sequelae caused by cerebral infarction include post-stroke depression, anxiety, aphasia, pathological effects, catastrophic reaction, mood and behavior psychosis, cognitive disorders, etc. *Cortex* 8:41-55 (1972); *Int. J. Ger. Psych.* 2(4):211-221 (1997); *Psychosomatics* 41(1):5-14 (2000). ✓

The degree of the severity of the mood disorders which occur after the stroke depends on the injured region. For example, post-stroke depression accompanies a left-hemispheric injury and proximity to the frontal pole, and mania or bipolar conditions accompany a right-sided lesion. *Int. J. Psychiatry Med.* 25(1):39-51 (1995). ✓

The incidence of post-stroke depression is about 20% at about 1 month after the stroke and 30 to 40% at 1 year after the stroke. *Eur. Psychiatry* 12 (suppl. 3):255S-260S (1997). ✓

In the National Institute of Neurological Disorders and Stroke, Classification III of the cerebrovascular disorders, the following symptoms of stroke, as well as diagnoses and treatments thereof, are described. *Stroke* 21(4):674-675 (1990).

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

Cognitive Status: In chronic stage, severe cognitive limitations, as well as less obvious deficits in higher-order function (e.g., judgment, planning, reasoning) and visual perception may require evaluation with detailed neuropsychological testing. Depression due to organic changes in the brain or to reactive factors occurs following a stroke.

Communicative Capabilities: Stroke patients with communication problems are categorized as having aphasia, dysarthria, or apraxia. Most standardized examination are for aphasia.

Functional Abilities: Physical abilities, daily living functional activities.

Nimodipine is one of the agents which was subjected to clinical studies for treatment of sequelae caused by cerebral infarction. Nimodipine was orally administered (90 mg/day) for 12 weeks to patients at 7 to 14 days after ischemic stroke and found to improve the cognitive disorders which appear in the chronic stage of the ischemic stroke. *Acta Neurol. Scand.*, 97(6):386-392 (1998).

In addition, nortriptyline, which is a tricyclic anti-depression agent, was subjected to a double-blind study for about 6 weeks in patients with depression (262 \pm 437 days after the ischemic stroke in the case of nortriptyline-administered group and 128 \pm 190 days after the ischemic stroke in the case of a control group). It was found that the nortriptyline-administered group showed apparent improvements in the depression score. *Lancet* 1:297-300 (1984). ✓

C. Differences between treatments of acute stage ischemic stroke and cerebral infarction sequela

As explained above, disorders caused by cerebral infarctions are classified into two groups: one comprising neurological and motor functional disorders, resulting from the direct

2002年 1月17日 11時04分

山之内製薬 (株) 特許センター

448 P. 9/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

injuries of the neuronal cells caused by the ischemia (those seen in acute stage ischemic stroke), and the second comprising neuropsychiatric and neuroethological disorders which are found in the chronic stage (sequelae caused by cerebral infarction).

The disorders that are found in the chronic stage, i.e., disorders which are generally accepted as the sequelae caused by cerebral infarction, generally include (1) disorders in speech and cognition and (2) mental disorders such as depression and hallucination. Importantly, if early stage treatments are not carried out, only rehabilitation is available as a therapy for mental disorders and motor functional disorders. Indeed, cognitive disorders are treated by the anti-dementia agents or the like, and mental disorders are treated by anti-psychotic agents and anti-depression agents.

The agents for treating acute stage ischemic stroke, which have been approved or under clinical trials in the United States, are agents that are administered within a short time period (e.g., several hours or days) after the stroke in order to inhibit the progression of the infarct region. Such treatment is expected to reduce the occurrence of mental disorders and motor functional disorders.

In contrast, there is no agent which has been approved in the United States as an agent for treating sequelae caused by cerebral infarction *per se*, i.e., no agent has been identified for repairing the damage done after the progression of the infarct region during the acute stage. As mentioned above, anti-dementia agents, anti-psychotic agents, anti-depression agents, and the like are only useful in the treatment of the sequelae which occur in the chronic stage.

'2002年 1月17日 11時04分

山之内薬工株式会社

0448 P. 10/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

Thus, as is clear from this discussion, the agents for treatment, the patients to be treated, the duration of the administration, and the objects of the treatment are quite different between acute stage ischemic stroke and sequelae caused by cerebral infarction.

III. JPA '844 does not teach or suggest the present invention

Neither JPA '884, or references cited therein, teach or suggest the use of a compound exhibiting mGluR1 antagonism in the treatment of acute stage ischemic stroke according to the present invention.

Indeed, JPA '884 merely discloses a compound having mGluR1 antagonism that is useful for treating the conditions of sequelae caused by cerebral infarction. There is no disclosure in JPA '884 that a mGluR1 antagonist would be useful in the treatment of acute stage ischemic stroke. And as explained above, one skilled in the art would not reasonably expect that an agent useful in the treatment of sequelae caused by cerebral infarction would also be useful in the treatment of acute stage ischemic stroke, due primarily to the different goals of each treatment and the completely different physiological effect of the different treatment agents.

As for the references cited in JP '884, the following is a discussion of the most relevant references, demonstrating that none of the teach or suggest the present invention.

a. *Annu. Rev. Pharmacol. Toxicol* 29:365 (1989) discloses that excitatory amino acid agonists cause conditions similar to the neuropathy resulting from ischemia.

b. *Trends Pharmacol. Sci.* 11:379 (1990) discloses that excitatory amino acid antagonists are effective for inhibiting acute toxicity. It is considered that the acute toxicity of the excitatory amino acids contributes to neuronal cell death after cerebral ischemia.

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

While these references might suggest the effects of the excitatory amino acid antagonist (a subordinate concept of mGluR1 antagonist) for inhibiting neurological disorders due to ischemia, a treatment for acute stage ischemic stroke is not disclosed.

The next group of references are cited as reporting mGluR antagonists which might be suggested to be related to neuronal cell death.

c. *Mol. Pharmacol.* 42:192 (1992) discloses that 1S, 3R-ACPD (a non-selective mGluR agonist) inhibits intracellular Ca^{2+} increase by AMPA, NMDA, KA, and enhances inward current.

d. *J. Neurosci.* 13:4445 (1993) discloses that 1S, 3R-ACPD injures cerebral nerves at a high dose.

e. *Trends Pharmacol. Sci.* 14:13 (1993) discloses that L-AP3 acts as a weak rat mGluR1 antagonist. Intraocular injection of 1S, 3R-ACPD protects against retinal change induced by NMDA.

The above references do not teach the inhibition of neuronal cell death by mGluR1 antagonists. The references which may, at the most, teach the *in vitro* effect of mGluR agonists in the induction of neuronal cell death, do not teach or suggest the effect of a mGluR1 antagonist to treat acute stage ischemic stroke.

IV. No previous disclosure of the use of a mGluR1 antagonists in treating acute stage ischemic stroke

Prior to the priority date of March 3, 1998, of the present application, there is no reference which discloses the effects of mGluR1 antagonists in treating acute stage ischemic stroke.

2002年 1月17日 11時04分

山之内製薬株式会社

0448 P. 12/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

The following are references relating to compounds that exhibit *in vitro* neuronal cell death inhibiting effects.

- a. *Brain Res.* 772:45-56 (1997) discloses that the administration of 1S, 3R-ACPD (a mGluR agonist) to rat striatum causes neuronal cell death at 10 days after administration.
- b. *J. Brain Res.* 38:317-322 (1997) discloses that the administration of (S)-DHPG, which is a Group I mGluR agonist, to rat hippocampus, resulted in no change in the number of cells at 8 hours after the administration, but that neuronal cell death was found at 1 to 3 days after the administration.
- c. *Neurosci. Lett.* 202:109-112 (1995) discloses that the administration of (S)-4C3HPG, which is a Group I mGluR antagonist and Group II agonist, to rat striatum, inhibited neuronal cell death by quinolinic acid (NMDA agonist) but MCPG, which is a Group I mGluR antagonist and Group II mGluR antagonist, did not.
- d. *Neuropharmacology* 33:715-717 (1994) discloses that MCPG (a mGluR antagonist) inhibited cell death in CA1 neurons of sliced rat hippocampus by hypoxia and hypoglycemia conditions.
- e. *TINS* 19(7):267-271 (1996) suggests that from the results of d., Group I antagonists would be neuroprotective against cerebral ischemia or acute neurodegeneration.

As described above, the *in vitro* neuronal cell death induced by mGluR agonists and the ability of Group I mGluR antagonist to inhibit neuronal cell death by glutamate toxicity, does not teach or suggest the ability of a mGluR I antagonist to effectively treat acute stage ischemic stroke.

2002年 1月17日 11時05分

山之内製薬 (株) 特許部

0448 P. 13/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appln. No. 09/601,505

Q60247

The following references relate to compounds that exhibit *in vivo* neuronal cell death inhibiting effects.

(1) The ability of compounds to inhibit neuronal cell death induced by agents.

a. *J. Neurosci.* 13:4445-4455 (1993) discloses that the administration of 1S, 3R- *
ACPD to neonatal rat induces neuronal cell death.

b. *Neurodegeneration* 4:71-80 (1995) discloses that the administration of 1S, 3R- /
ACPD to rats causes neuronal cell injury in the hippocampus CA1 region at 4 hours after
administration, and vacuolation of the CA4 region at 8 hours after the administration.

Induction of neuronal cell death by the administration of a mGluR agonist, which has an
activity opposite that of mGluR1 antagonists, does not teach or suggest the ability of a mGluR1
antagonist to effectively treat acute stage ischemic stroke.

(2) Cerebral ischemia model - global cerebral ischemia model

The following references reported the effect of mGluR1 antagonists in global cerebral
ischemia models.

a. *Eur. J. Pharmacol.* 282:259-262 (1995) which discloses that in a gerbil global /
cerebral ischemia model (transient ischemia: 5 min.), L-AP3, a mGluR1 antagonist, inhibited
* neuronal cell death at 4 days after the occlusion.

b. *Society for Neuroscience Abstracts* 23:788.2 (1997) and *E. Neuropharmacol.* 7(2),
S.09.03 1997 which disclose that in the gerbil global cerebral ischemia model (5 min. ischemia),
AIDA, which is a mGluR1 antagonist, inhibits neuronal cell death found in the CA1 region. *

2002年 1月17日 11時05分

山之内製薬株式会社

0448 P. 14/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

c. *Society of Neuroscience Abstracts* 23:756.8 (1997) which discloses that in the gerbil global cerebral ischemia model (5 min. ischemia), 4C3HPC (Group I antagonist and Group II agonist) was administered at 5 minutes before ischemia or at 15 minutes after ischemia, and a neuroprotective effect was reported as the finding at 7 days after ischemia.

However, such "global cerebral ischemia" models suffer from a serious defect and the results of such studies cannot be interpreted to be indicative of potential *in vivo* results.

Cerebral infarction occurs by the occlusion of main arteries in the brain due to various reasons. Due to the difference of the occluded arteries, a pathology of so-called "focal cerebral ischemia" occurs (characteristic infarct patterns occur which are unique to the specific cerebral regions). The relationship between the duration of the reduced regional cerebral blood flow and the degree of cellular injuries has been well studied. In relation to the focal cerebral ischemia, spatial regions are observed depending on the degree of existence of collateral blood vessels (i.e., dependence on the blood flow from the occluded artery), that is, from the ischemic core region (the region which has the highest ischemia severity and which is liable to display irreversible disorders) to the surrounding reversible disorder region (penumbra).

Because clinical ischemic stroke occurs as "focal cerebral ischemia," the pathophysiology is quite different from the global cerebral ischemia models in which uniform and short-time blood flow decrease is allowed to occur (*Geemfield's Neuropathology* 4th ed., 125-156, eds. Adams, J.H. et al., Edward Arnold, London, 1984; *Stroke*, 12:723-725 (1981); *Ann. Neurol.* 36:557-565 (1994)).

2002年 1月17日 11時05分

山之内 敬 (山之内 敬)

0448 P. 15/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

Accordingly, the technical level at the time the present invention, namely March 3, 1998, was a model which is quite different from acute stage ischemic stroke. Accordingly, these models do not teach or suggest the effects for acute stage ischemic stroke.

(3) Focal cerebral ischemia model - Ischemic stroke model

References which use a focal cerebral ischemic model similar to the present invention include the following.

a. *Eur. J. Pharmacol.* 216:335-336 (1992) which discloses that in a rat focal cerebral ischemia model, tACPD, which is a mGluR agonist, reduced the cerebral infarct volume at 7 days.

This reference reported that the mGluR agonist reduced the cerebral infarct volume, which teaches away from the present invention, which relates to a mGluR antagonist useful in the treatment of acute ischemic stroke.

b. *Neuroscience* 79(1):1-5 (1997) which discloses that in mouse ischemia model (MCAo model), administration of MGPG at 5 minutes before the occlusion did not reduce the infarct volume at 24 hours after the occlusion.

(4) Other models

Progress in Neuro-Psychopharmacology & Biological Psychiatry 20:1253-1263 (1996) discloses that in a rat hypoxia model, administration L-AP3 and MCPG, which are the mGluR antagonists, at 30 minutes before the hypoxic condition, inhibited neuronal cell death at 4 days thereafter.

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

The rat hypoxia model utilizes a different pathology from focal cerebral ischemia. Further, the ability of a mGluR1 antagonist to treat acute stage ischemic stroke is not taught or suggested.

Accordingly, as is evident from the detailed analysis and explanations above, it is apparent that, even in view of JPA '884 and the technical level at the date of JPA '884, the use of the agents disclosed therein for treating acute stage ischemic stroke according to the present invention is not taught or suggested.

In summary, none of JPA '884 and the references discussed above teach or suggest the present invention.

V. The present invention is unobvious

A. *The references do not suggest the ability of mGluR1 antagonist to treat acute stage ischemic stroke*

As described above, the global cerebral ischemia model cited in JPA '884 does not render obvious the ability of a mGluR1 antagonist to treat acute stage ischemic stroke as claimed in the present invention to one of ordinary skill in the art.

This position is supported by the fact that Valproate, which is effective for the gerbil 5-minute bilateral common carotid artery occlusion model (global cerebral ischemia model), is not effective in the cerebral infarction model (focal cerebral ischemia model) (not effective in the transient MCAo model: *Epilepsia* 38:975-980 (1997); effective in the gerbil model: *Stroke* 20:281-287 (1989)). ✓

Moreover, it is important to note that with respect to the animals used as the model, it was reported that there are various agents which are effective in the gerbil model, but are not

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

effective in the models of other animals, and that the gerbil model should not be used for the evaluation of the efficacy of the agents for acute stage ischemic stroke. *Stroke* 20:2752-2758 (1999).

In addition, *Eur. J. Pharmacol.* 216:335-336 (1992) reported that t-ACPD, which is a ^{*}mGluR agonist, reduced the infarct volume in the rat focal ischemia model.

Furthermore, it was reported in *Society of Neuroscience* 79(1):1-5 (1997) that MCPG, ^{*}which has Group I and Group II antagonism, did not exhibit the ability to inhibit infarct volume in the rat and mouse cerebral ischemia models.

These reports deny the motivation based on the known effects in the global ischemia model to anticipate the effect of mGluR1 antagonists on the acute stage ischemic stroke according to the present invention.

Accordingly, the effect which was shown by using the gerbil global cerebral ischemia model does not render obvious the ability of a mGluR1 antagonist to treat acute stage ischemic stroke as claimed in the present invention.

Thus, JPA '884 clearly does not make the present invention obvious to one of ordinary skill in the art.

B. Long-felt need

As further support for the non-obvious nature of the present invention, there has been a long-felt need for compositions such as those disclosed in the present invention.

Stroke is the third leading cause of death in advanced nations. Among the victims of stroke, 20% die within 30 days after the onset and 4 to 60% of the surviving patients suffer from

2002年 1月17日 11時06分

山之内製薬株式会社

0448 P. 18/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appl. No. 09/601,505

Q60247

the sequela. Known treatments of acute stage stroke are (1) general therapy which mainly include controls of patients' overall conditions (rest, respiration control, blood pressure control, fluid replacement, etc.) and (2) conservative treatment in compliance with the pathology and prevention of complications such as pneumonia, infections, phlebothrombosis, pulmonary embolism, decubitus, arthrogryposis, etc.

Recent fundamental and clinical evidences suggest that early stage treatment, immediately after the onset of the disease, can make it possible to sustain life and reduce the occurrence of disorders. As a matter of fact, it has been shown that treatment with t-PA within 3 hours after acute ischemic stroke onset can improve the mortality and prognosis. However, Alteplase has been confirmed to be effective only for those cases where it is administered within 3 hours after the onset of ischemia and thus the applicable cases are limited.

With the exception of Alteplase, almost no country has approved agents for improving the mortality and neurological symptoms during acute stage treatment. Thus, such a medicament has been keenly demanded and many pharmaceutical companies are conducting research and development for such a medicament. There is a high demand to develop an agent for treating acute stage ischemic stroke which inhibits neuronal cell death during the acute stage of cerebral ischemia as much as possible, and also has a neuroprotective effect to inhibit expansion of infarct region (*Lancet* 352 (suppl III):1-30; *Science* 272:664 (1996)). ✓

Thus, in view of points discussed above, the technical level at the time the present invention was made in March, 1998, and the long-felt need in this area of technology, the present

2002年 1月17日 11時06分

山之内 隆夫 特許センター

0448 P. 19/19

DECLARATION UNDER 37 C.F.R. §1.132
U.S. Appln. No. 09/601,505

Q60247

invention is not obvious over JPA '884, or the references cited therein, to one of ordinary skill in the art.

VI. Conclusion

Finally, I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

January 17, 2002
Date:

Masamichi Okada
Name: Masamichi OKADA